Application of Life Stage Specific Data in the Risk Assessment for Children: Case Study Presentation Using Pesticides

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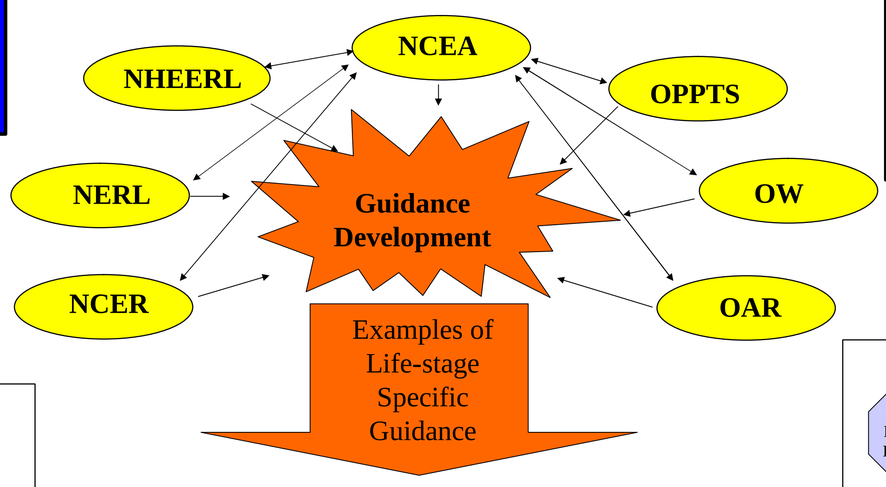
Atrazine and Chlorpyrifos

- Widely-used pesticides with documented potential for exposure to children.
- Were undergoing program office risk assessments.
- ORD input was essential to the interpretation of life-stage specific susceptibility and was critical to the assessment of risk to children's health.
- Extensive collaboration and consultation between ORD and the Program Offices occurred during the process of developing the risk assessments.

Background

ORD has historically contributed to the risk assessments of specific individual pesticides or classes of pesticides through:
- Test methods development
- Generation of data
- Consultation with the Program Offices.

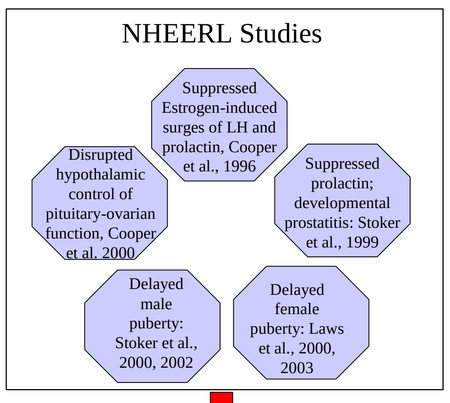


ORD Research

Research conducted or supported by ORD contributed to characterization of life-stage specific susceptibility issues for each of these two chemicals.
- Atrazine: Identified the critical non-cancer mode of action (MoA) for risk assessment, i.e., disruption to the hypothalamic-pituitary-gonadal axis during development.
- Chlorpyrifos: Characterized age-related sensitivity of behavioral endpoints and cholinesterase inhibition, and the assessment of children's exposure to chlorpyrifos was developed and/or refined.

ATRAZINE

Registrant-Generated Toxicology and Exposure Data



Critical non-cancer MoA for risk assessment identified: disruption to the hypothalamic-pituitary-gonadal axis during development

Atrazine – Interim Reregistration Eligibility Decision (2003)

Exposure Scenario	Dose (NOAEL)	Endpoint	Study
Acute Dietary Females 13-50	10 m/k/d	Delayed ossification (NOAEL supported by prostatitis in male offspring, Stoker et al., 1999)	Developmental rat and rabbit
Chronic Dietary	1.8 m/k/d	Attenuated LH surge as biomarker for hypothalamic disruption	6-mo LH surge
Short-term Dermal/Inhalation	6.25 m/k/d	Delayed preputial separation	Pubertal assay (Stoker et al., 2000)
Intermediate-Term Dermal/Inhalation	1.8 m/k/d	Attenuated LH surge as biomarker for hypothalamic disruption	6-mo LH surge

Public perception of potential risk was refocused away from cancer and onto neuroendocrine-mediated reproductive/developmental risks from atrazine exposure to susceptible populations

Risk Assessment Guidelines
Developmental Tox, revised, 1994
Reproduction, 1996
Neurotoxicity, 1998
Carcinogenicity (draft), 1999

Guidance Documents
FQPA/10X Task Force, 1999
Review of the RfD and RfC Processes, 2002
Child-Specific Exposure Factor Handbook, 2002
Children's Health Risk Assess. Framework, in progress

OPPTS Test Guidelines
Developmental Tox, revised, 1998
Reproduction/Fertility, revised, 1998
Developmental Neurotox, revised, 1998
Developmental Immunotox, in progress

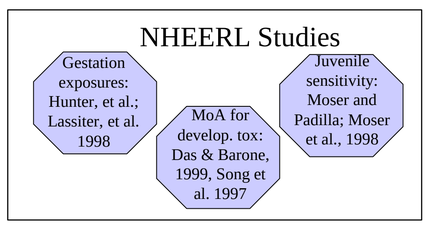
Life-Stage Specific Methods Development
Biomarker assays
Endocrine assays

Puberty Studies

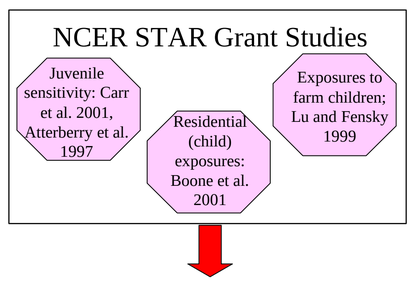
ChEI Data

ORD development of risk assessment (RA) guidelines and guidance has advanced the state of the knowledge in specific scientific areas, e.g., susceptibility, and has provided a strong link between ORD research and chemical risk assessment. This has resulted in higher quality, defensible decision-making by the Program Offices and greater consistency in cross-Agency risk assessment practices.

CHLORPYRIFOS



Registrant-Generated Toxicology and Exposure Data



Age-related sensitivity was characterized for the established MoA (cholinesterase inhibition - ChEI)

Chlorpyrifos – Reregistration Eligibility Decision (2000)

Exposure Scenario	Dose (NOAEL)	Endpoint	Study
Acute Dietary	0.5 m/k/d	Plasma and RBC ChEI	Blood time course study
Chronic Dietary	0.03 m/k/d	Plasma and RBC ChEI	WOE: 2-yr dog; 90-d dog; 2-yr rat; 90-d rat; DNT
Short-term Dermal	0.15 m/k/d	Plasma and RBC ChEI	21-d dermal rat
Intermediate/Long Term Dermal	0.03 m/k/d	Plasma and RBC ChEI	WOE: 2-yr dog; 90-d dog; 2-yr rat; 90-d rat; DNT

Based upon information on sensitivity and susceptibility of the young, and on residual uncertainties regarding potential adverse effects following exposure of children to chlorpyrifos, the 10X FQPA Safety Factor was applied to all children's health risk assessments for chlorpyrifos.

A number of residential uses of chlorpyrifos were cancelled or limited; public awareness of potential risks to susceptible populations was raised; preliminary data suggest positive outcomes on these populations (Whyatt et al. 2004)

Outcome and Impact

Risk management decisions made by the Program Offices addressed the protection of susceptible populations.
- **Chlorpyrifos:** Residential uses were cancelled in mitigation efforts that became effective in 2001. Earlier CDC biomonitoring studies suggest that levels of urinary metabolites that are indicative of chlorpyrifos exposure are lower in the 1999-2000 period compared to the 1988-1994 period. Additionally, in an NCER-supported study of an urban minority cohort of newborn babies and their mothers (Whyatt et al., 2004), levels of chlorpyrifos in personal air and blood samples were substantially decreased from 1998-2002, and correlations between chlorpyrifos exposure levels and decreased birth weight/length observed in 1998 were no longer apparent in 2002.
- **Atrazine:** Risk communication efforts were critical in refocusing public perception of potential risks, away from long-term cancer concerns (the focus of past risk assessments) and towards non-cancer risks to susceptible populations.

ORD Contribution to Program Office Risk Assessments

For the atrazine and chlorpyrifos risk assessments, ORD research provided:
- Confirmation of susceptibility in the young
- Support for decisions regarding the adverse consequences of the observed effects
- A basis for extrapolation from animal data to potential human response
- Methodologies to assess exposure to children
- Information critical in identifying the point of departure for risk assessments conducted by OPP and OW.

Atrazine References:
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Chlorpyrifos References:
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